I. Priority

Applicants acknowledge the Examiner's granting the benefit of priority for the U.S. Provisional Application No. 60/123,167 filed on March 5, 1999.

II. Information Disclosure Statement

Applicant acknowledges the review of the information disclosure statement filed on June 19, 2000 (Paper No. 2). Applicant notes that the information disclosure statement filed on May 4, 2001 (Paper No. 3), and resulting from a case related to the present case has not been reviewed. Applicant will attend to the filing of a supplemental information disclosure statement under separate cover.

III. Objections to the Specification

The Examiner objects to the Title for not completely describing the invention. In response Applicants have amended the Title herein to read "Methods and Compositions for Inhibiting Apoptosis Using Serine Protease Inhibitors".

IV. Objections to the Claims

The Examiner objects to claims 8 and 25 due to various informalities. These informalities are rendered moot through the amendments set forth herein.

V. Rejections Under 35 § 112, ~~first~~ second paragraph

Claims 1-18 are rejected under 35 U.S.C 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Specifically, the examiner objects to use of the term

"excessive apoptosis". In response Applicants have amended the claims such that they are now directed either to a method of inhibiting apoptosis or to a method of treating a selected group of diseases, wherein the listed diseases are characterized as diseases involving excessive apoptosis.

The Examiner objects to claims 3, 4, and 22 as containing the following allegedly unclear terms: α1-antitrypsin-like agent; variant of α1-antitrypsin-like; anticathepsin G agent; antitryptase TL2-agent; antifactor Xa agent; antielastase agent; antiproteinase-3 agent.

Applicants traverse. Applicants submit that each of these terms are readily known by those skilled in the art. Further, each of these terms relates to serine protease inhibitors.

α1-antitrypsin-like agent relates to a non-natural molecule that inhibits serine protease.

Variant of α1-antitrypsin-like relates to an agent that is altered from the natural molecule, but possesses activity.

Cathepsin G is a serine protease and a pANCA antigen. The cathepsins belong to a group of intercellular proteases mainly found in the lysosomes. Thus, an anticathepsin G agent is an agent that inhibits cathepsin G.

Tryptase is a tetrameric serine protease seen in mast cells. Tryptase TL2 is a T cell associated serine protease. Antitryptase TL2-agent is thus an agent that inhibits tryptase TL2.

Factor Xa is a protease, which cleaves the arginine residue in the preferred cleavage site Ile-(Glu or Asp)-Gly-Arg. Antifactor Xa agent is thus an agent that inhibits factor Xa.

In addition to a wide variety of protein substates, elastase will also hydrolyze elastin. An antielastase agent is thus an agent that inhibits the serine protease known as elastase.

Proteinase-3 is a serine protease found for example in azurophil granules of human polymorphonuclear leukocytes. Antiproteinase-3 agent is thus an agent that inhibits proteinase-3.

The Examiner also objects to claims 4, 9, 12-14, 16 and 24 due to the use of the term about. Applicants have amended the affected claims, thereby rendering this objection moot.

The Examiner objects to the use of the term BTD in claims 8 and 25. To expedite prosecution, the claims have been amended, rendering this objection moot.

The Examiner objects to the use of the term buccally in claim 15. Applicants traverse, buccal is known by those of skill in the art to mean relating to the cheek or mouth cavity. Thus, to administer buccally would mean to administer via cheek or mouth cavity.

The Examiner objects to claim 18, stating that the phrase "exhibiting mammalian α-antitrypsin or α-antitrypsin-like activity" does not clearly define what compounds to use and that the level of inhibitory activity is undefined. Applicants traverse. Alpha-1 antitrypsin is a protein synthesized in the liver and immediately secreted into the blood where it acts as an antiprotease (protease inhibitor Pi). Thus, claim 18 is directed to an agent that exhibits this type of activity. The level of inhibitory activity required is that

amount which would be sufficient to provide the effects set forth in the Figures and Examples of the specification. See for example Figures 1 and 2, and corresponding text.

Lastly, the Examiner objects to claim 24, stating that it is unclear how blood concentrations are related to inhibitor concentrations in a cell. Applicants note that antitrypsin does not go inside the cell. Rather, the agent works outside of the cell. Applicants note that the claim reads: "providing a serine protease inhibitor to a cell", it does not read "providing a serine protease inhibitor inside a cell." The claim has been amended to more particularly point out and distinctly claim that subject matter which Applicants regard as the invention.

Applicants believe that these amendments address the Examiner's concerns under 35 U.S.C. 112, second paragraph. Reconsideration of the rejection and withdrawal thereof is respectfully requested.

III. Rejections Under 35 § 112, first paragraph

The Examiner has rejected claims 1-18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to enable one skilled in the art to make and/or use the invention. The Examiner, for example cites to the fact that apoptosis inhibitors are not clearly set forth in the art as cancer treatment. Applicant agrees that an apoptosis inhibitor would generally not be indicated in the treatment of cancer. Indeed, with cancer one is concerned with cell proliferation and the absence of cell death. One would not want to inhibit apoptosis in such a case. Rather this invention is directed toward inhibiting apoptosis. This is desired in those conditions characterized by excessive cell death; such as wasting disease, neurodegenerative disease, myocardial infarction, stroke, Alzheimer's disease, arthritis, muscular dystrophy, Downs Syndrome, sepsis, HIV infection, multiple sclerosis, arteriosclerosis, diabetes, arthritis, autoimmune disease, ischemia-reperfusion injury, or toxin-induced liver injury.

Applicants direct the Examiner to Figure 1 relating to the effect of α_1–antitrypsin on apoptosis in primary rat brain cerebral granule cells and Figure 2 illustrating the effect of α_1-antitrypsin and the peptoid CE-2072 on apoptosis in RCG Neuron (rat cerebral

granule) cells. Applicants also direct the Examiner to Page 15, line 29 through Page 19, line 5 of the specification.

The Examiner also rejects claims 6 and 23 stating that while the specification, while possibly being enabling for using derivatized serine protease inhibitors that retain the inhibitory activity, does not reasonably provide enablement for derivatized serine protease inhibitors that no longer function to inhibit serine protease. Applicants submit that the amendments provided herein render this objection moot.

The Examiner has rejected claims 19-20 stating that the specification, while being enabling for *reducing* apoptosis in cell or tissue culture, does not reasonably provide enbalement for *inhibiting* apoptosis in cell or tissue culture. Applicant notes that reduce and inhibit are synonyms. Inhibit does not mean to stop all activity. Rather it means to lessen the level of activity. In practicing the present invention, one would wish to lessen the level of activity to a therapeutically efficacious level.

The Examiner rejects claims 21-25, stating that while being enabling for using certain serine protease inhibitors to inhibit some forms of apoptosis, the specification does not provide enablement for using all serine protease inhibitor to inhibit all forms of apoptosis. However, the C.C.P.A. has stated that the specification need not contain a working example of every embodiment of the invention "if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to pratice it." *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). *See, United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988).

Applicant has amended and provided new claims to more particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. Applicant believes that these amendments and the remarks provided herein address the Examiner's concerns under 35 U.S.C. 112, first paragraph. Reconsideration of the rejection and withdrawal thereof is respectfully requested.

IV. Rejections Under 35 § 102

On page 6 of the Office Action, the Examiner rejects claims 21-22 under 35 U.S.C. 103(a) as being anticipated by van Molle. The Examiner states that van Molle

teaches the inhibition of TNF-induced apoptosis using α1-antitrypsin in mouse hepatocytes.

Applicants submit that this reference is not relevant art. The van Molle reference relates to tumor necrosis factor induced apoptosis and not to subjects suffering from various disease states characterized by excessive apoptosis. Thus, the teaching of this document is that antitrypsin inhibits TNF activity. Further, the von Molle reference does not provide any disclosure related to synthetic mimetics.

In view of the foregoing amendments and remarks, it is believed that this application is in condition for allowance. A notice to this effect is respectfully requested.

AUTHORIZATION

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment to Deposit Account No. 50-1710.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and withdraws them. There being no other objections or rejections, Applicant respectfully requests that the present application be allowed and pass to issue.

Should any further questions arise concerning this application, the Examiner is invited to call Applicants' attorney at the number listed below.

Respectfully submitted,

Gilberto M. Villacorta, PH.D.
Registration No. 34,038

for Gianna Julian Arnold 35,753
Gianna Julian Arnold
Registration No. 36,358

Patent Administrator
KATTEN MUCHIN ZAVIS ROSENMAN
525 West Monroe Street, Suite 1600
Chicago, Illinois 60661-3963
Fax: (312) 906-1021
(202) 625-3500
Date: May 14, 2002

APPENDIX

MARKED-UP VERSION TO SHOW CHANGES MADE

The specification is amended as follows:

Page 1, line 1, after "Inhibiting Apoptosis" please insert -- Using Serine Protease Inhibitors--.

Page 7, line 8, after "these diseases are" please delete --cancer--.

The claims are amended as follows:

1. (Amended) A method of inhibiting apoptosis in a subject, [treating a subject suffering a disease characterized by excessive apoptosis] comprising:

administering a therapeutically effective amount of at least one serine protease inhibitor in which the effective amount inhibits [excessive] apoptosis;

wherein the subject suffers from at least one of wasting disease, neurodegenerative disease, myocardial infarction, stroke, Alzheimer's disease, arthritis, muscular dystrophy, Downs Syndrome, sepsis, HIV infection, multiple sclerosis, arteriosclerosis, diabetes, arthritis, autoimmune disease, ischemia-reperfusion injury, or toxin-induced liver injury.

4. (Amended) The method of claim 3 in which the effective amount is [between about 0.3 and about 7.0] greater than 0.2 and less than 8.0 g/kg body weight.

6. (Amended) The method of claim 5, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation, and wherein the derivatized serine protease inhibitor retains the inhibitory activity.

8. (Amended) The method of claim 1, in which the serine protease inhibitor is selected from the group consisting of:

(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl) carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[T]trifluoro methylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[M]methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[T]thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-([P]phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

[and] ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[P]phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;[,]

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide[,];

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazoly]carbonyl)- 2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-Dimethylamino benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-napthylenyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-napthylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

2-(5-[([B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)- (S)-2-methylpropyl]acetamide;

2-(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5- (3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

2-(5-[([B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(S)-2-methylpropyl]acetamide;

2-(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5- (3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-methylpropyl]acetamide;

([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)]-1,2,4-oxadiazolyl)-(S)-methylpropyl]amide;

(2S,5S)-5-[A]amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl -N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(R,S)-2-methylpropyl]amide;

[BTD-][1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

(R,S)-3-[A]amino-2-oxo-5-phenyl-1,4,-benzodiazepine-N-[1-(2-(5-(3-methylbenzy l)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

[A]acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

3-(S)-([B]benzyloxycarbonyl)amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzy l)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-(S)-([A]amino)- ε--lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt;

3-(S)-[(4-morpholino carbonyl-butanoyl)amino]- ε--lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3, 4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide;

6-[4-[F]fluorophenyl]- ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

2-(2-(R,S)-[P]phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]hydroxymethyl)-2-(S)-methylpropyl]acetamide;

2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-acetamide;

2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl oxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2- (R,S,)-methylpropyl]acetamide;

(1-[B]benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

(1-[B]benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

(1-[P]phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

[(1-[P]phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)]-2-(S)-methylpropyl]acetamide;

3-[([B]benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-[([B]benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-([C]carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methybenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-([A]amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-[(4-[M]morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1, 3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3,4-[D]dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[A]acetyl-3-(4-fluorobenzylidene) piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[A]acetyl-3-(4-dimethylamino benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-[A]acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[A]acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methyl benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3-(R)-benzyl-piperazine-2,5,-dione]-N-[1-(2 -[5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3(R)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[M]methyl-3-(R,S)-phenylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[[-[M]methyl-3-(R,S)-phenyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
4-[1-(4-[M]morpholino ethyl)3-(R)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R,S)-[P]phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1 ,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;
[and] 1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethyl benzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide, pharmaceutically acceptable salts thereof, and combinations thereof.

9. (Amended) The method of claim 8, in which the effective amount is [between about 0.001 and about 7.0] at least 0.001 and less than 8.0 g/kg body weight.

12. (Amended) The method of claim 1, in which the therapeutically effective amount is sufficient to provide [about 10 pM to about 2 mM] at least 8 pM and less than 3 mM of the inhibitor in the biological fluid of the subject.

14. (Amended) The method of claim 1, in which the therapeutically effective amount is sufficient to provide [about 5 μM to about 200 μM] at least 2 μM and less than 220 μM in the biological fluid of the subject.

16. (Amended) The method of claim 1, in which the therapeutically effective amount is administered [between about once daily to about once hourly] at least once daily.

21. (Amended) A method of inhibiting apoptosis, comprising providing a serine protease inhibitor to at least one cell and measuring a decrease in apoptosis.

23. (Amended) The method of claim 22, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation, and wherein the derivatized serine protease inhibitor retains the inhibitory activity.

24. (Amended) The method of claim 23, wherein the at least one cell is a cell of a subject, [in which] and wherein the amount is sufficient to bring the concentration of serine protease inhibitor in the subject's blood to [between about 5 μM to about 200 μM] at least 2 μM and less than 220 μM.

25. (Amended) The method of claim 21, in which the serine protease inhibitor is (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
(benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl) carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[T]trifluoro methylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[M]methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[T]thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-([P]phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

[and] ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[P]phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;[,]

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide[,];

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazoly]carbonyl)- 2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-Dimethylamino benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-napthylenyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl] carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-napthylmethylene)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

2-(5-[([B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)- (S)-2-methylpropyl]acetamide;

2-(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5- (3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

2-(5-[([B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(S)-2-methylpropyl]acetamide;

2-(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5- (3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-methylpropyl]acetamide;

([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)]-1,2,4-oxadiazolyl)-(S)-methylpropyl]amide;

(2S,5S)-5-[A]amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl -N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-(R,S)-2-methylpropyl]amide;

[BTD-][1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

(R,S)-3-[A]amino-2-oxo-5-phenyl-1,4,-benzodiazepine-N-[1-(2-(5-(3-methylbenzy l)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

[A]acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]amide;

3-(S)-([B]benzyloxycarbonyl)amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzy l)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-(S)-([A]amino)- ε--lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt;

3-(S)-[(4-morpholino carbonyl-butanoyl)amino]- ε--lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3, 4-oxadiazolyl]carbonyl)-2-(R,S)-methylpropyl]acetamide;

6-[4-[F]fluorophenyl]- ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

2-(2-(R,S)-[P]phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]hydroxymethyl)-2-(S)-methylpropyl]acetamide;

2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4 -oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-acetamide;

2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl oxide]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2- (R,S,)-methylpropyl]acetamide;

(1-[B]benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

(1-[B]benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

(1-[P]phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

[(1-[P]phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4 -oxadiazolyl]carbonyl)]-2-(S)-methylpropyl]acetamide;

3-[([B]benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-[([B]benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-([C]carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methybenzyl)-1,3,4-oxadiazoly l]carbonyl)-2-(S)-methylpropyl]acetamide;

3-([A]amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3-[(4-[M]morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1, 3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

3,4-[D]dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[A]acetyl-3-(4-fluorobenzylidene) piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[A]acetyl-3-(4-dimethylamino benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 1-[A]acetyl-3-(4-carbomethoxy benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[A]acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methyl benzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3-(R)-benzyl-piperazine-2,5,-dione]-N-[1-(2 -[5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3(R)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-Benzyl-3-(S)-benzylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[B]benzyl-3-(S)-benzyl piperazine-2,5,-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-[M]methyl-3-(R,S)-phenylpiperazine-2,5,-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[[-[M]methyl-3-(R,S)-phenyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

4-[1-(4-[M]morpholino ethyl)3-(R)-benzyl piperazine-2,5,-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide; 5-(R,S)-[P]phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1 ,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1 ,3,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide;

1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethyl benzyl)-1,2,4-oxadiazolyl]carbonyl)-2-(S)-methylpropyl]acetamide, pharmaceutically acceptable salts thereof, or combinations thereof.